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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 11/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/825,012	YOUNG, ROBERT	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) *23-28,32,39 and 43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-7, 9-20, 22, 29-31, 33-37* is/are rejected.

7)☐ Claim(s) *8 and 21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 3, 7, 16, 19, 20, 39 and 40 have been amended. Claims 2 and 38 have been canceled. Claims 23-28 and 32 remain withdrawn from consideration. Claims 39 and 43 are also withdrawn from consideration as depending upon non-elected claim 32. Claims 1, 3-22, 29-31, 33-37 are under consideration.

2. Sections of Title 35 U.S. code not found n this action can be found in a previous action.

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 31-37 are rejected under 35 U.S.C. 101 because they are not presented in the format of a proper process claim. See MPEP 2173.05(q).

5. Claims 14, 20, 30, 31 and 33-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) Claims 31 and 33-37 drawn to the "use" of an active agent are vague and indefinite. The claims are drawn to a method of using an agent, but fail to set forth any active, positive steps that define the claimed method..

(B) Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 20 refers to amino acid sequences encoded by nucleotide sequences of figure 3 and figure 5. Section 2173.05(s) of the MPEP states

> Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience." Ex parte Fressola, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993) (citations omitted).
> Reference characters corresponding to elements recited in the detailed description and the drawings may be used in conjunction with the recitation of the same element or group

of elements in the claims. See MPEP § 608.01(m).

Thus, the claims are rendered vague and indefinite in that they are not complete in themselves as a result of relying on Figures within the specification. Amendment of the claims to recite the SEQ ID NO of the nucleotide or amino acid sequences would overcome this rejection.

(C) It is unclear how claim 30 further limits the scope of claim 1. The recitation of "for use in medicine" is an intended use and cannot be linked with a physical or functional attribute of the compound of claim 1 which would further limit the scope of claim 1.

(D) Claim 14 recites "the amino acid sequence shown in Sequence ID's 3 and 4 or (b)". It is unclear what is meant by "(b)". Further Sequence ID NO:4 is not an amino acid sequence.

6. The rejection of claims 1-3, 7 and 8 under 35 U.S.C. 102(a) as being anticipated by Young et al (Proceed Amer Assoc Cancer Res, March 2000, Vol..41, page 289, reference of the IDS filed January 23, 2003) is withdrawn in light of applicants Declaration under 37 C.F.R. 1.132.

7. Claims 1, 3-7, 9, 10, 13, 15, 17-20, 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Epenetos et al (WO 94/15644, reference of the IDS filed January 23, 2003) in view of Schlom (In: Molecular Foundations of Oncology, 1991, pp. 95-134), Van Hoft et al (Cancer Research, 1996, Vol. 56, pp. 5179-5185) and Verhoyen et al (WO 92/04380, reference of the IDS filed January 23, 2003).

Claim 1 is drawn to a compound comprising a target sell-specific portion and a cytotoxic potion characterized in that the target cell-specific portion comprises a humanized monoclonal antibody having specificity for PEM or an antigen binding fragment thereof and the cytotoxic portion has endonucleolytic activity, wherein the target-specific portion comprises a humanized HMFG-1 antibody or an antigen-binding fragment thereof. Claim 3 embodies the compound of claim 1 wherein the target cell specific portion is a humanized HMFG-1 antibody. Claim 4 embodies the compound of claim 1 wherein the target cell specific portion comprises and antigen-binding fragment of the humanized antibody selected from the group consisting of Fab-

like molecules, Fv molecules, disulphide-linked Fv molecules, scFv molecules and single domain antibodies. Claim 5 embodies the compound of claim 4 wherein the target cell specific portion comprises a Fab a molecule. Claim 6 embodies the compound of claim 4 wherein the target-specific portion comprises a F(ab')2 molecule. Claim 7 embodies the compound of claim 1 wherein the target cell portion comprises an antigen-binding fragment encoded by at least part of one or both of the nucleitde sequences of SEQ ID NO:7 and 10-12. Claim 9 embodies the compound of claim 1 wherein the cytotoxic compounds has DNA endonucleolytic activity. Claim 10 embodies the compound of claim 9 wherein the cytotoxic portion is at least the catalytically active portion of a DNA endonuclease. Claim 13 embodies the compound of claim 1 wherein the endonuclease is a restriction endonuclease. Claim 15 embodies the compound of claim 1 having a nuclear localization signal. Claim 17 embodies the compound of claim 1 wherein the target-cell specific portion and the cytotoxic portion are fused. Claim 18 embodies the compound of claim 17 wherein the target-cell specific portion and the cytotoxic portion are separated by a linker sequence. Claim 19 embodies the compound of claim 18 wherein the linker sequence is or comprises GG or GSGG. Claim 30 embodies the compound of claim 1 for use in medicine.

Claim 29 is drawn to a pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier.

Epenetos et al teach a compound comprising a target cell specific portion and a cytotoxic portion characterized in that the cytotoxic portion has DNA endonucleolytic activity (page 3, lines 12-17), and specifically that the DNA endonuclease could be a type II restriction endonuclease (page 27, lines 8-11) thus fulfilling the specific embodiments of claims 9, 10 and 13. Epenetos et al teach the incorporation into the compound a nuclear targeting sequence (page 28, lines 23-26) thus fulfilling the specific embodiments of claims 15 and 16. Epenetos et al teach that the entity which is recognized by the target cell specific portion is an entity which is expressed by tumor cells and will often be recognized as an antigen, examples of which are set forth in Table 1 (page 6, lines 1-7). Table 1 includes PEM (page 10) which is recognized by the antibody HMFG1. Epenetos et al teach that the antibody could be a Fab-like molecule, Fv molecules, scFv and single domain antibodies (page 7, lines 1-10) or a humanized antibody (page 6, lines 20-23), thus fulfilling the specific embodiments of claims 4, 5 and 6. Epenetos et

al teach the fusion of a target cell specific portion with a cytotoxic portion by means of a synthetic linker, Gly-Gly-Gly-Gly-Ser-Gly (page 41, lines 10-13), thus fulfilling the specific embodiments of claim18 and claim 19 because the linker of comprises GG. Epenetos et al teach that a reagent which hydrolyses DNA would be particularly advantageous to rapidly dividing cells, such as tumor cells because during mitosis the nuclear membrane is dissolved and the cellular DNA is exposed (page 28, lines 16-21). Epenetos et al teaches the subject matter of claims 7 and 20 because "at least part" can read on a single amino acid. Epenetos et al do not specifically teach the a compound comprising the HMFG1 antibody and a DNA endonuclease.

Schlom teaches that an immunotoxin is effective when internalized (page 107, second column, lines 5-10, under the heading "Drug and Toxin Conjugates"). Schlom teaches that it is unrealistic to assume that just one or tow administrations of a anti-cancer therapeutic would be effective. Schlom points out that because of anti-HAMA responses against murine antibodies, only the first dose, and perhaps the second dose reached the tumor target. Schlom teaches that a solution to this problem is a humanized antibody (page 98, second column, line 29 to page 99, first column, line 4).

Van Hoft et al teach that the product of the MUC-1 gene, termed PEM, is internalized continuously, and therefore is a suitable antigen for antibody-directed therapy (page 5179, second column, first full paragraph).

Verhoyen et al teach humanization of the HMFG1 antibody (for example, page 21, line 19 to page 22, line 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to fuse the humanized HMGF1 antibody or an PEM-binding fragment thereof to a DNA endonuclease with endonucleolytic activity or human deoxyribonuclease I for treatment of tumors expressing PEM. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Epenetos et al regarding PEM as a target antigen and HMFG1 as the antibody which specifically binds to PEM; the teachings of Van Hoft regarding the internalization of PEM, and the teachings of Schlom regarding the effectiveness of immunotoxins which are internalized; the teachings of Schlom regarding the HAMA response to murine antibodies resulting in loss of delivered anti-tumor agent which is circumvented by the use of humanized antibodies and the teaching of

Verhoyen et al on the humanization of HMFG1. One of skill in the art would be motivated to use humanized HMFG1 or a PEM binding fragment thereof in a fusion protein with a DNA endonuclease in order to delver the DNA endonuclease to tumor cells expressing the PEM antigen and undergoing rapid mitosis, because on of skill in the art would know that the binding of an antibody to the PEM antigen will result in the translocation of the antibody to the cytoplasm of the cell; one of skill in the art would also know that tumor cells are be more susceptible to a DNA endonuclease that cells not undergoing rapid mitosis because of the teachings of Epenetos et al regarding the nuclear membrane. One of skill in the art would also be motivated to use a human deoxyribonuclease n order to avoid an immune response against a bovine deoxyribonuclease. One of skill in the art would understand that the teachings of Schlom regarding the HAMA response against murine antibodies would also apply to an immunotoxin wherein the toxin portion was a non-human protein. One of skill in the art would be motivated to prevent an immune response against both the antibody portion and the cytotoxic portion of the immunotoxin so that the full dose of the compound would be available to the patient during a course of treatment involving multiple injections with the compound.

Applicant argues that the disclosure of Schlom teaches away from the instant invention because Shlom teaches an alternate method of avoiding the inherent limitations of targeting an internalizing antibody by stating that Schlom teaches that the immunoconjugate should be designed to disassociate at the target cell periphery and the cytotoxic agent to be then transported into the cell. This has been considered but not found persuasive. Firstly, Schlom concludes that because some [emphasis added] solid tumor membrane antigens are stable cell surface components suggests that a subset [emphasis added] of mAb drug conjugates will be ineffective against these target antigens (page 107, second column, lines 10-14 under the heading "Drug and Toxin mAb Conjugates"). Clearly one of skill in the art would conclude that this was not the case for the PEM antigen after reading the teachings of Applicant does not state the line and page number within the Schlom reference where such a disclosure was made. Applicant argues that Schlom teaches against the targeting of cellular internalizing receptors because of the statement of Schlom "The above limitations may not apply, however if the chemical bond utilized to link the drug to the immunoglobulin is sufficiently labile to permit disassociation of the cytotoxic agent at the tumor cell periphery followed by transport into antigen-positive or nearby antigen

negative cells" (page 107, second column, lines 18-24 under the heading "Drug and Toxin mAb Conjugates"). Applicant is incorrect in assuming that Schlom is teaching against the targeting of immunotoxins to internalizing receptors. Further, applicant is also incorrect in assuming that one of skill in the art would target the claimed DNA endonucleases in such a manner, because one of skill in the art would know that said endonucleases will not be able to penetrate the cell membrane as is the case of a small drug molecule, such as the vinca alkaloid taught by Schlom (page 107, second column, lines 26-28 under the heading "Drug and Toxin mAb Conjugates"). In that case, the small drug molecule can be attached to an antibody which would concentrate in the area of the target tissue but release the cytotoxic drug within the target area without relying upon an internalizing receptor. That is not the case with the instant cytotoxic moieties which are large proteins such as DNA endonucleases. These proteins would not be able to be taken up by the cells as a small molecule drug. Further, this teaching in no way renders Schlom incompatible with the instant invention. Schlom teaches that an immunotoxin is effective when internalized (page 107, column two, lines 5-10 under the heading of "Drug and Toxin Conjugates"). Thus, one of skill in the art would be strongly motivated to target and internalizing receptor to allow for internalization of an immunotoxin.

Applicant argues that Schlom fails to teach any other toxin than ricin A. This argument is unpersuasive. Firstly applicant does not identify the page and line number where this is stated. Applicant should note that Schlom teaches that anti-tumor antibodies can be modified by directly ligating the anti-tumor molecule or a linker for an anti-tumor molecule directly into the Ig molecule and that this has been accomplished in the ligation of the Pseudomonas endotoxin into mAb OVB3 and anti-TAC (page 119, first column, lines 27-36). One of skill in the art would recognize that on page 108, first column) Schlom is reviewing [emphasis added] the clinical trials with immunotoxins as of 1991, and the teachings of Epenetos were relied upon for motivation to use DNA endonucleases not the specific cytotoxic moieties as taught by Schlom.

Applicant argues that van Hoft teaches away from the instant invention because van Hoft teaches that a portion of the PEM antigen is shed from the tumor and therefore only a portion of the PEM antigen would be available fro binding with the antibody. This is not found persuasive. Van Hoft concludes that PEM is internalized continuously and therefore is a suitable agent for antibody-directed therapy (page 5179, second column, lines 3-6). It is further noted that van

Hoft teaches the administration of a radio labeled antibody which targeted PEM in vivo. In table 5 on page 5183 it is noted that the ratio of the radio labeled antibody in the tumor tissue versus the blood was 2:1 at 6 days post administration. One of skill in the art would construe from this fact that it is possible to target the PEM on the tumor tissue in spite of the fact that some PEM is shed from the tumor into the blood. Applicant's arguments are moot regarding this point.

Applicant argues that Verhoyen teaches only ricin A as a compound for use in an immunoconjugate. This is not persuasive because Verhoyen was relied upon only for teachings regarding the humanization of HMFG-1.

8. Claims 1, 3-7, 9-15, 17-20, 29 and 30are rejected under 35 U.S.C. 103(a) as being unpatentable over Epenetos et al, Schlom, Van Hoft et al, and Verhoyen et al as applied to claims 1, 3-7, 9, 10, 13, 15, 17-20, 29 and 30 above, and further in view of the abstract of Linardou et al (Cell Biophysics, 1994, Vol. 24-25, pp. 243-248).

Claim 11 embodies the method of claim 10 wherein the endonuclease is a mammalian DNAseI. Claim 12 embodies the method of claim 11 wherein the endonuclease is a human DNAseI. Claim 14 embodies the method of claim 10 wherein the cytotoxic portion comprises the amino acid sequence of SEQ ID NO:3.

The combination of Epenetos et al, Schlom, Van Hoft et al, and Verhoyen et al render obvious the instant claims with respect to a DNA endonuclease and a DNA endonuclease which is a restriction endonuclease. Neither of the references teaches a method wherein the DNA endonuclease is specifically a mammalian or human DNAse I.

The abstract of Linardou et al teaches that immunoconjugates made with mammalian DNAseI avoid the immunogenicity associated with using a non-mammalian toxin linked to an antibody.

It would have been prima facie obvious to substitute a mammalian or human DNAseI in place of the restriction endonuclease taught by Epenetos et al. One of skill in the art would be motivated to use a mammalian DNAseI in place of the restriction endonuclease taught by Epenetos et al because a mammalian or human enzyme would have less immunogenicity in a human undergoing immunotherapy, and because Schlom specifically teaches the used of humanized antibodies to avoid an immune reaction against an administered antibody, because it

will be necessary to administer the antibody more than once during a course of cancer therapy. One of skill ion the art would be motivated to make an immunotoxin which is non-immunogenic both in the cell-targeting portion and in the portion responsible for cytotoxicity so that said immunotoxin will not loose efficacy during a treatment protocol involving multiple administrations of the immunotoxin.

9. Claims 1, 3-7, 9, 10, 13, 15-20, 29 and 30are rejected under 35 U.S.C. 103(a) as being unpatentable over Epenetos et al, Schlom, Van Hoft et al, and Verhoyen et al as applied to claims 1, 3-7, 9, 10, 13, 15, 17-20, 29 and 30 above, and further in view of the abstract of Kalderon et al (Cell, 1984, Vol. 39, pp. 499-509).

Claim 16 embodies the compound of claim 15 wherein the nuclear localization signal is PKKKRKV. Epenetos et al teach the use of a nuclear localization signal for targeting of the DNA endonuclease into the nucleus of the cancer cell. Epenetos et al do not specifically teach the PKKKRKV nuclear localization signal.

The abstract of Kalderon et al teaches the PKKKRKV nuclear localization signal.

It would have been prima facie obvious at the time the invention was made to exchange the nuclear localization signal of Epenetos et al for the nuclear localization signal of the abstract of Kalderon et al. One of skill in the art would have been motivated to do so because one of skill in the art would know that both the nuclear localization peptide of Epenetos et al and the nuclear localization peptide of Kalderon et al will function to direct the DNA endonuclease into the nucleus of the cancer cell.

10. The rejection of claims 1-7 and 13 under 35 U.S.C. 103(a) as being unpatentable over Epenetos et al (WO 94/15644, reference of the IDS filed January 23, 2003) in view of Pietersz et al (Cancer Immunol Immunother, 1997, Vol. 44, pp. 323-328) is withdrawn in light of applicants amendment specifying that the target-cell specific portion is a HMFG-1 antibody or an antigen-binding fragment therefore.

11. Claims 8 and 21 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

12. All other objections and rejections as set forth in the previous Office action are withdrawn in light of applicants amendments.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
10/31/2004

KAREN A. CANELLA PH
PRIMARY EXAMINER